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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/642,363	08/14/2003	Jong-Wan Park	13100-02CIP	1639

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EXAMINER	
ROBERTS, LEZAH	
ART UNIT	PAPER NUMBER
1614	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/642,363	PARK ET AL.	
	Examiner	Art Unit	
	Lezah W. Roberts	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-20 and 26-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-20 and 26-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the Request for Continued Examination filed June 22, 2007. All previous rejections have been withdrawn unless stated below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims

Claim Rejections - 35 USC § 112 – Written Description (New Rejection)

Claims 7-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims recite the limitation R1 is a polyol.

The specification states that R1 is a polyol in the compound of Formula 1. Polyol is defined as "a substance with multiple hydroxyl groups, and includes sugars (reducing and nonreducing sugars), sugar alcohols and sugar acids. Preferred polyols herein have a molecular weight, which is less than about 600 kD (e.g. in the range from about 120 to about 400 kD)." Although the definition names certain groups of polyols, it does not limit polyol to these particular groups because the definition uses the term "includes" and not "are". The sugars disclosed as polyols are broad classes of molecules and encompass more sugars than that are disclosed as examples. The compounds with the polyol moiety are disclosed to inhibit HIF-1a expression in tumor cells, inhibit HIF-1-

regulated gene expression in tumor cells and tissues, inhibit angiogenesis in tumor cell or tissues, inhibiting tumor growth, inhibiting tumor progression and metastasis and treating an HIF-1-mediated disorder or condition. Nowhere, however, does it specify which particular compounds have the desired characteristic of selectively inhibiting HIF-1a expression in tumor cells, HIF-1-regulated gene expression in tumor cells and tissues, angiogenesis in tumor cell or tissues, tumor growth, tumor progression and metastasis and treating an HIF-1-mediated disorder or condition, other than sugars are fructose, mannose, maltose, lactose, arabinose, xylose, ribose, rhamnose, galactose, glucose, sucrose, trehalose, sorbose, melezitose, raffinose, mannitol, xylitol, erythritol, threitol, sorbitol, glycerol, L-gluconate, and metallic salts thereof. What the inventors did not do is succeed in taking the last, critical step of actually isolating compounds having other polyols and incorporating them on to the compound of Formula I at the R1 position, or at least of developing a process through which one skilled in the art would be directly led to such other compounds. See Univ. of Rochester v. G.D. Searle, 68 USPQ2d 1424, 1430-33 (DC WNY 2003).

The appearance of mere indistinct words in a specification or a claim (here the word polyol), even an original claim, does not necessarily satisfy the written description requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. Univ. of Rochester v. G.D. Searle, 69 USPQ2d 1886, 1892 (CAFC 2004). The examiner recognizes that the fact situation in the Rochester cases was extreme, with Applicant there disclosing no (or possibly one) specific compounds. The reasoning provided by the court can be fairly

extended to less extreme situations (*i.e.*, where a limited number of species is actually disclosed, such as here), however, given the court's recognition (Rochester (2003) at 1431) that:

> [I]n claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus.

As was the case in Rochester, there is no such specificity here, nor could one skilled in the art identify any particular compound, other than compounds of Formula I comprising a R1 moiety with the sugars listed above.

2) Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claim recites "treating an HIF-1-mediated disorder of condition".

The appearance of mere indistinct words in a specification or a claim (here HIF-1-mediated disorders), even in an original claim, does not necessarily satisfy the written description requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. Univ. of Rochester v. G.D. Searle, 69 USPQ2d 1886, 1892 (CAFC 2004). The specification states that HIF-1-mediated disorder or conditions include hepatoma, stomach carcinoma, renal

carcinoma, cervical carcinoma, neuroblastoma, and prostate carcinoma. The specification fails to disclose any other HIF-1-mediated disorders such as blood disorders associated with HIF-1 mediation.

Claim Rejections - 35 USC § 112 – Lack of Enablement

1) Claims 7-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the inhibition of tumor growth with the mannose YC-1 derivative, does not reasonably provide enablement for inhibiting HIF-1 α expression in tumor cells or tissues, inhibiting tumor growth, inhibiting HIF-1-regulated gene expression, inhibiting angiogenesis in tumor cells or tissues, inhibiting tumor progression and metastasis treating a HIF-1- mediated disorder or condition by all polyol YC-1 derivatives claimed. The rejection is maintained.

A) Applicant argues that it is the burden of the Office to provide objective reasons why enablement is not present. Therefore it is improper to shift the burden to Applicants to prove the presence of enablement. Applicants submit that the position that "testing one polyol derivative with one test such as tumor growth does not provide substantial evidence that all polyol derivatives will be effective" is misplaced because Lee et al. and Yeo et al. do not negatively impact the presumption of enablement in the instant application and the statement appears to improperly require additional "test" with other compounds to establish the presence of enablement. In regards to Lee et al., it is immaterial to the instantly claimed subject matter because Lee is testing for anti-platelet activity, which is not related to the subject matter of the instant claims. Therefore it is

only speculation that Lee et al.'s screens for anti-platelet activity raise doubts regarding the HIF-1 inhibiting activity of the derivatives featured in the pending claims.

Yeo et al. supports the presumption of enablement because the claimed subject matter is very closely related to YC-1. The compounds of the instant claims differ from YC-1 at the R1 moiety. There is no evidence that the presence of such a moiety has any negative effect on the HIF-1 inhibiting ability of the compounds. To the contrary, Example 10 and Figure 16 of the instant application clearly demonstrate that the presence of a representative polyol moiety on the compounds did not remove the HIF-1-mediated anti tumor activity.

It is improper for the Office to require additional "test" or "a representative set of the polyol derivatives encompassed by the claims because there has been no objective reason provided to cast doubt on the presence of enablement. No objective reason has been given for why the assumption that all derivatives of YC-1 will exhibit the same behavior as one derivative. Applicant further asserts that the presence of a small moiety on one end of the compounds would not negatively affect their HIF-1-inghibiting activity.

Applicants point out that the ultimate determination is whether undue experimentation is needed to make and use the claimed invention. The absence of complete predictability is clearly permitted, and the presence of routine and/or repetitive experimentation is the opposite of undue experimentation. There is an expectation that additional compounds modified only by the addition of an R1 polyol moiety would retain the same anti-HIF-1 activity, and so the level of unpredictability is acceptable. No more than routine and/or repetitive experimentation is needed to screen additional tumor cells

for the expression of HIF-1, indicating that they would be susceptible to the compounds of Formula I, and to confirm the HIF-1 inhibitory activity of the compounds encompassed by Formula I.

B) The Examiner has provided reason as to why enablement is not present by reporting the results of Lee et al. as an example of how varying one group on a molecule can affect its activity. By changing one moiety on the YC-1 compound, the effect on the targeted therapy was changed. The activity will not be the same or there would be no need to make derivatives and all derivatives of the molecule would be obvious. Therefore it may be highly expected that not all the derivatives that are encompassed by Formula I with a polyol at R1 will work for the inhibition HIF-1. The term polyol is broad and encompasses molecules such as polyphenols. These compounds or moieties do not appear to be enabled by the instant disclosure. Therefore undue experimentation would be necessitated to determine what type of polyol is proper to use for the disclosed method and to determine how to make the compounds encompassed by the instant claims. In regards to the expectation that additional compounds modified only by the addition of an R1 polyol moiety would retain the same anti-HIF-1 activity, Applicant points out examples showing that the degree of activity is not the same. Furthermore the claims not only encompass a change in the R1 moiety but also R2 and R3, which also increases the unpredictability of the compounds of Formula I. This further increases the scope of the claims and raises issues of enablement. Applicant's conclusion that no more than routine and/or repetitive experimentation is needed to screen additional tumor cells for the expression of HIF-1,

indicating that they would be susceptible to the compounds of Formula I, and to confirm the HIF-1 inhibitory activity of the compounds encompassed by Formula I is unsupported. The cited art supports that undue testing is required because of the unpredictability of whether the derivative of a lead compound will be effective. To have to test or question whether a compound will have the desired activity is undue experimentation. Practically speaking testing is required in the cancer art and the amount of testing and the results cannot be predicted. This is supported by the references cited in this rejection and in the rejection in subsection 2.

2) Claims 7-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the inhibition of tumor growth with the mannose YC-1 derivative in hepatoma cells in a xenograft, does not reasonably provide enablement for inhibiting HIF-1α expression in tumor cells or tissues, inhibiting tumor growth, inhibiting HIF-1-regulated gene expression, inhibiting angiogenesis in tumor cells or tissues, inhibiting tumor progression and metastasis treating a HIF-1- mediated disorder or condition for all cancers by all polyol YC-1 derivatives claimed. The rejection is maintained an applied to claims 26-28.

A) Applicant points out that the claimed subject matter is not directed to the treatment of all cancers without limit. The claims feature the targeting of HIF-1 as present in tumor cells. There is no objective reason given as to why the targeting of HIF-1 in tumor cells would require undue experimentation. The news article used by the Examiner, discloses a drug that is structurally unrelated to Formula I and is immaterial

with respect to HIF-1 inhibition. The article by Gura suggests that model systems for discovery of anti-cancer drugs are not predictive. Applicant submit that no more than routine and repetitive experimentation is needed, especially where the model systems are used to screen drug compound of a defined structure such as those of Formula I, and where there is already evidence of efficacy in an in vivo model and knowledge of the targeted molecule (HIF-1) as important for tumor angiogenesis and tumor survival. The presence of enabled subject matter does not require absolute predictability or the absence of experimentation. The level of unpredictability is acceptable because the additional compounds are modified only at the R1 moiety. Furthermore screening additional tumor cells for expression of HIF-1 takes no more than routine and/or repetitive experimentation.

B) See Examiner's answer to the arguments above in subsection 1.

3) Claims 19-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of hepatoma with the mannose YC-1 derivative, does not reasonably provide enablement for the treatment of all HIF-1-mediated disorder or conditions in a mammal with all polyol YC-1 derivatives. The rejection is maintained.

A) Applicant argues that the claimed subject matter is not directed to the treatment of all cancers without limit. There is no objective reason given as to why the targeting of HIF-1 in mammalian cells would require undue experimentation. The article cited reports the drug endostatin and endostatin is structurally unrelated to the Formula

I and therefore immaterial with respect to HIF-1 inhibition. Gura is used to suggest that model systems for discovery of anti-cancer drugs are not predictive. The instant rejection fails to explain why use of the model system is equivalent to undue experimentation, especially where so many skilled practitioners in the field continue to use those very same model systems on a daily basis. There is no objective reason given as to why these articles are relevant to the inhibition of HIF-1 in a mammal or predictive of results with the use of Formula I compounds. The presence of enabled subject matter does not require absolute predictability or the absence of experimentation. There is expectation of success that additional compounds modified only by the addition of an R1 polyol moiety would result in the retention of the HIF-1 inhibiting activity. Therefore the level of unpredictability is acceptable. Furthermore screening mammals with a HIF-1-mediated disorder or condition for the effectiveness of the compounds of formula I in inhibiting HIF-1 takes no more than routine and/or repetitive experimentation. This argument is not persuasive.

B) The HIF-1-mediated conditions encompassed by the claims do not appear to be within the scope of the instant claims. The mediated disorders encompassed by the disclosure are primarily tumors. The articles are used to show the unpredictability of screening drugs for one category of HIF-1 disorders such as cancer. It may be concluded that this unpredictability is greater when more disorders are involved. Also see Examiner's answer to the arguments in subsection 1.

Claims 7-20 and 26-28 are rejected.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lezah W. Roberts whose telephone number is 571-272-1071. The examiner can normally be reached on 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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